بسم الله الرحمن الرحيم

السلام عليكم ورحمة الله وبركاته

Diabetic Nephropathy - Glycemic status
Relationship

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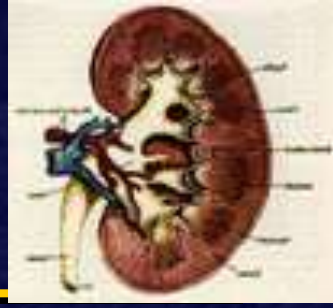
Objectives & Outlines

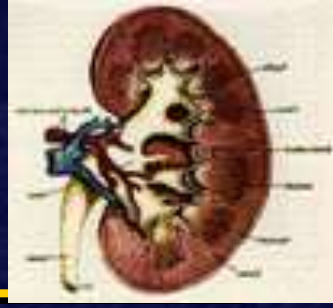
- SOME FACTS ABOUT DN
- ROLE OF HYPERGLYCEMIA IN DN
- GLYCEMIC CONTROL & DN

Diabetic Nephropathy



- A microvascular complication of diabetes marked by albuminuria and a deteriorating course from normal renal function to ESRD
- Clinical syndrome characterised by
  - Persistent albuminuria
  - On at least 2 occasions separated by 3 months

Diabetic Nephropathy

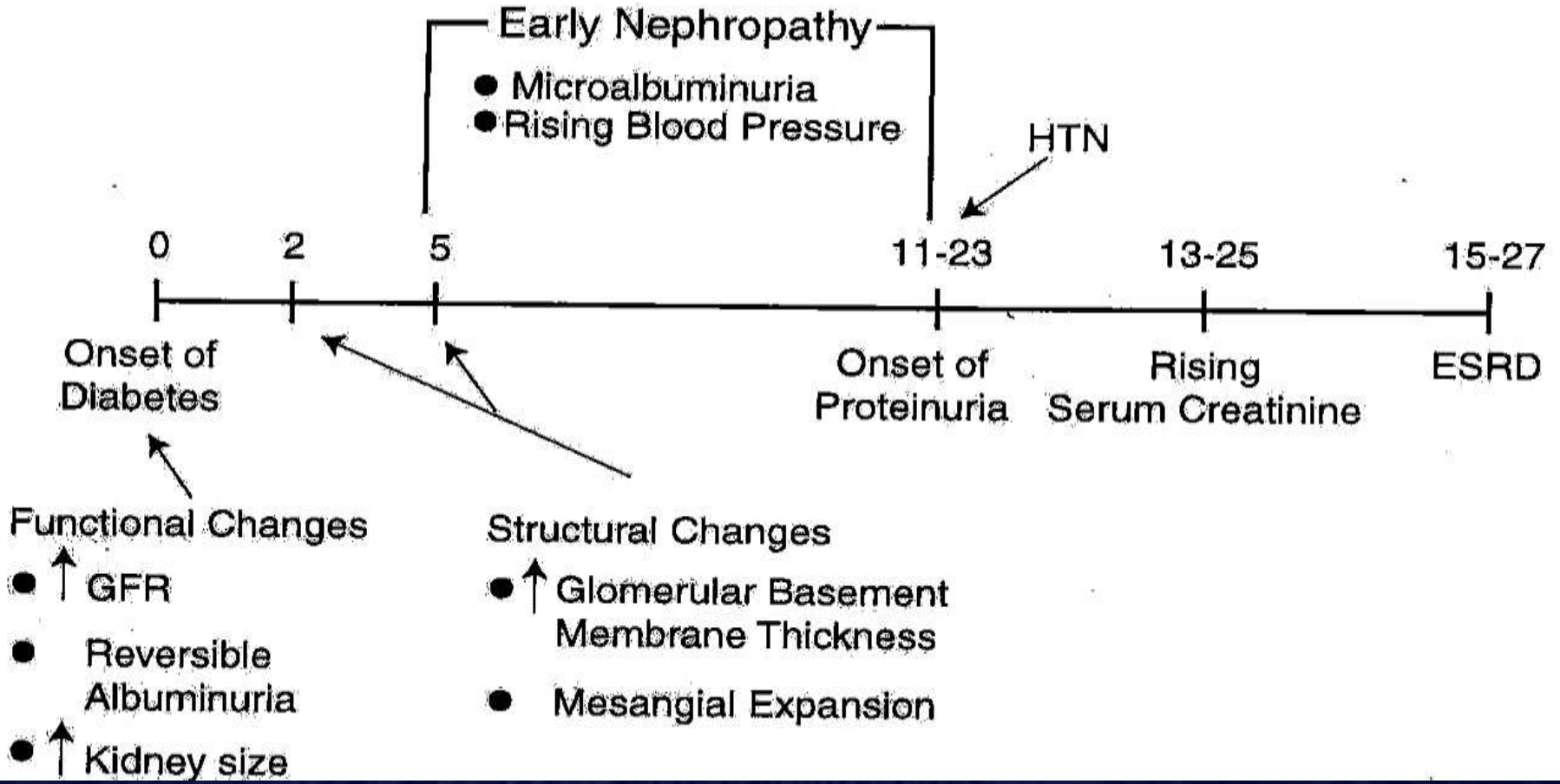


- Diabetes has become the most common single cause of ESRD in the US and Europe
- Accounts for over one-third of all patients who are on dialysis
- About 20–30% of patients with T1DM or T2DM develop evidence of nephropathy

Risk factors

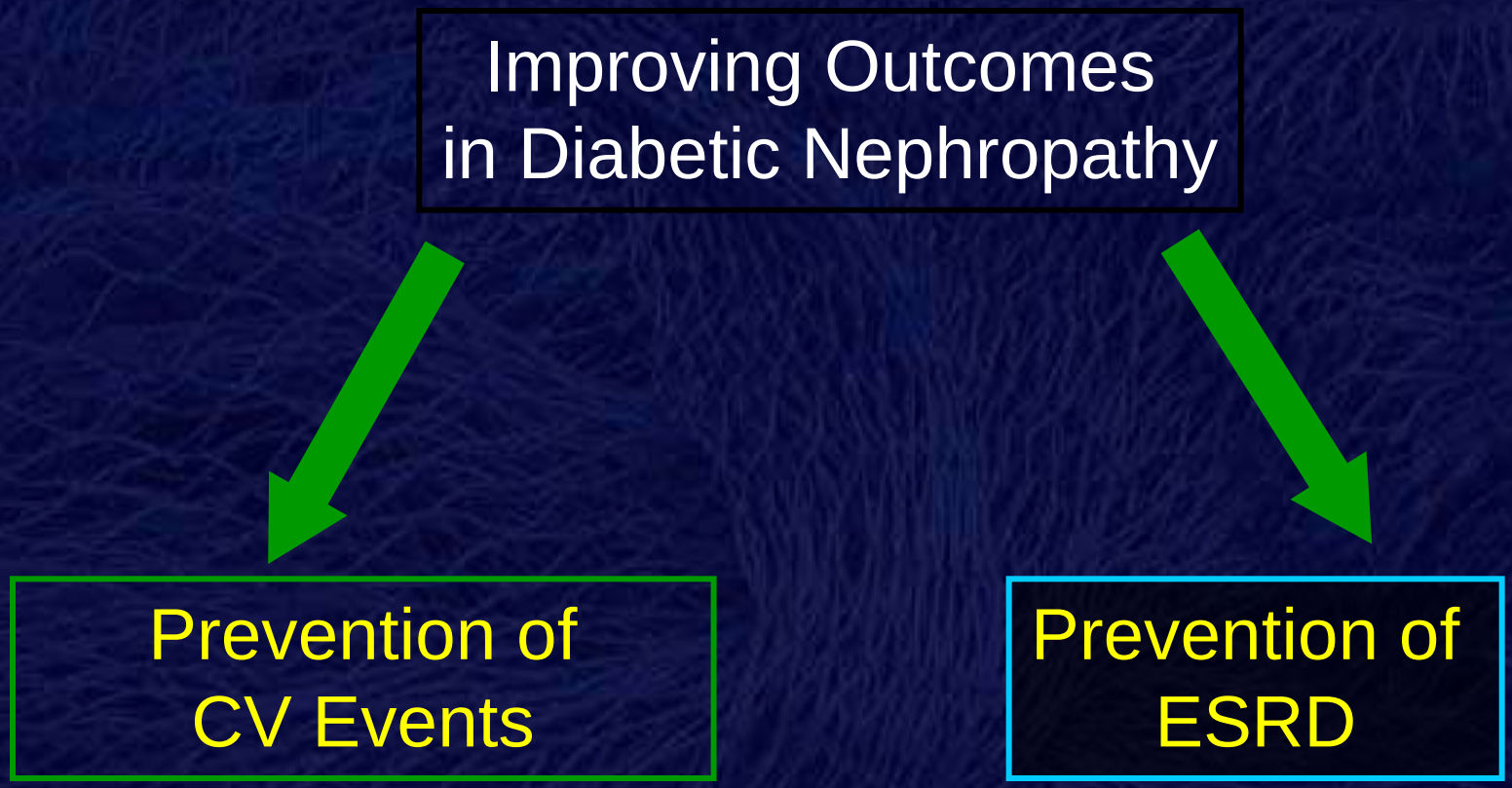
- DM Type & Duration
  - 20% of T1DM after 20 yrs
  - 40% of T2DM any duration
- **Poor glycemic control**
- Hypertension
- Ethnicity: Pima Indians (60%)
- Male gender
  - T1DM: M/F risk of DN 1.7:1
  - T2DM: M/F risk of DN 5:1
- Family history (ACE Gene, IL-1 & IL-1RN)
- Cigarette smoking
- Dyslipidemia
- Obesity

Natural History

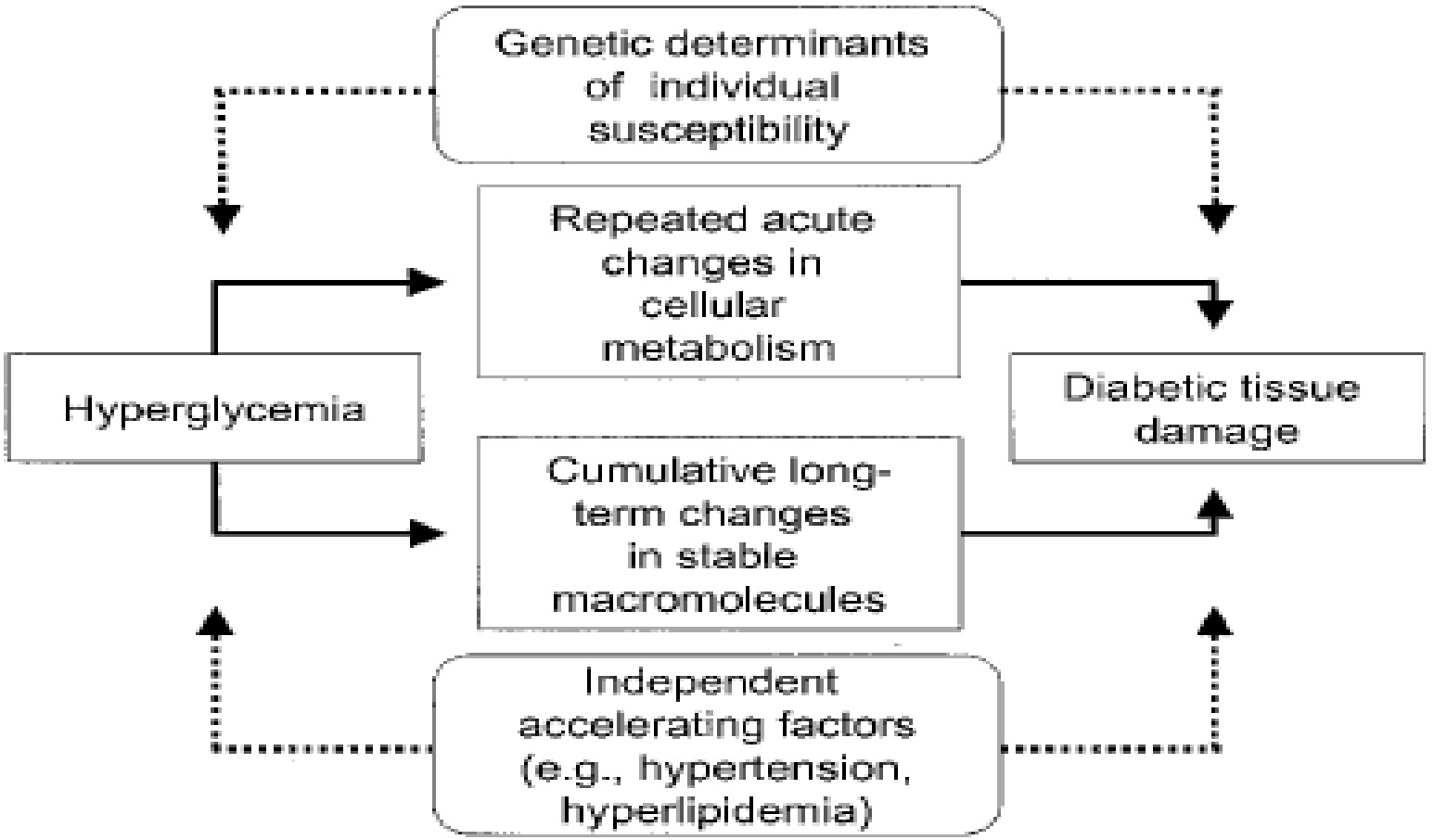


- CV Morbidity & mortality →→→→→→→→→→→→→→

Diabetic Nephropathy



Pathophysiology of microvascular complication



Brownlee M. Diabetes 54:1615, 2005

Pathophysiology of microvascular complication

- Chronic hyperglycemia
  - Initiating factor of microvascular diseases
  - Magnitude & duration => positively correlates to diabetic microvascular complication
- Hyperglycemia
  - ↑ Blood flow & intracapillary pressure, NO activity↓
  - ↑ ET-1, A II, VEGF permeability
  - ↑ Glomerular capillary damage and albumin excretion
  - Connective tissue growth factors: key molecules involved in the pathogenesis of fibrosing CKD

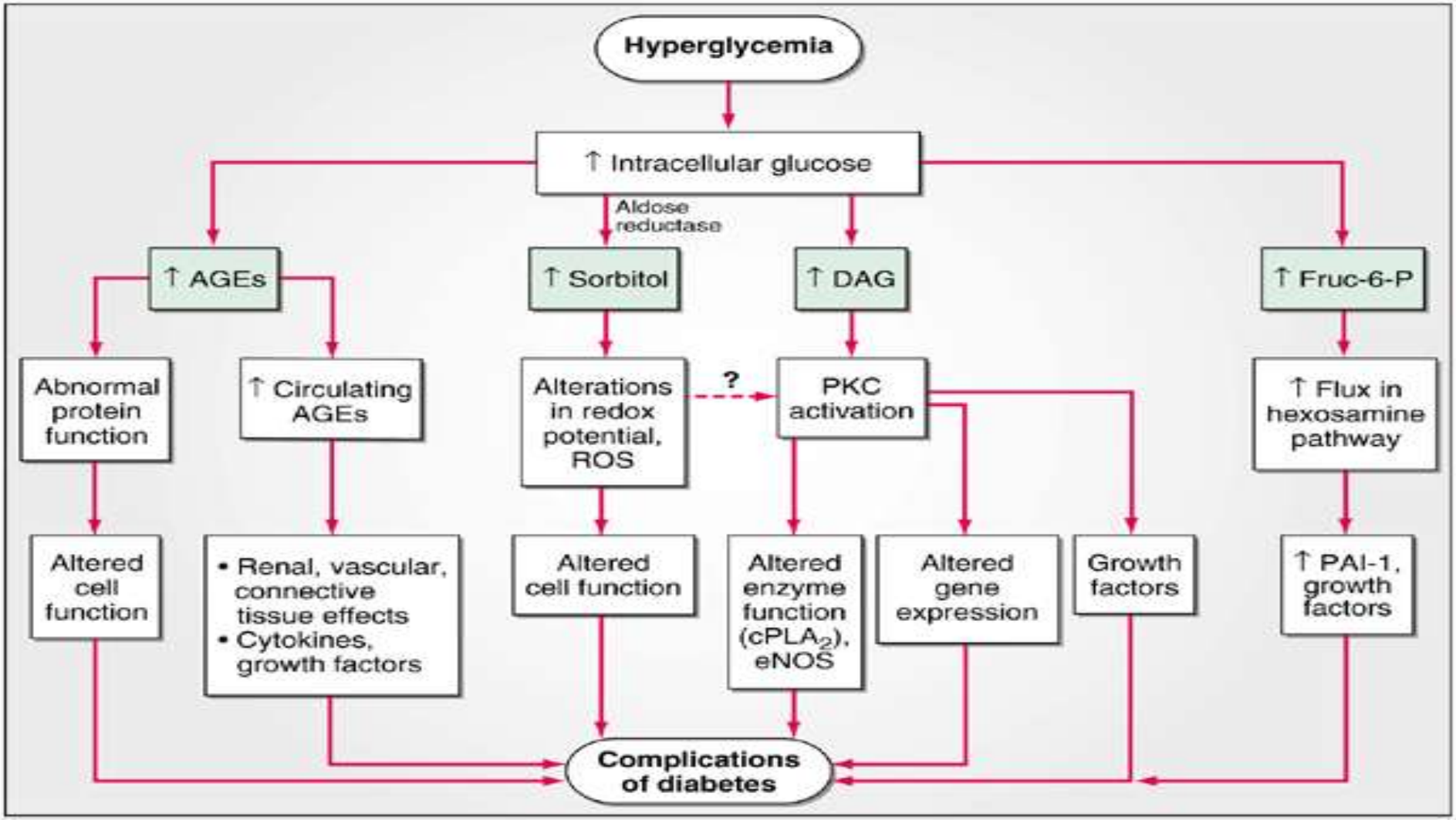
Pathophysiology of DN
Hyperglycemia

- Activation of PK C results in increased vascular Contractility; Cellular Proliferation & vascular Permeability
- Collagen IV deposition is directly stimulated by hyperglycaemia
- Cell culture studies have shown that glucose can induce Cell hypertrophy and extra cellular matrix production
- Result is increased renal filtration, leading to glomerular hypertrophy
- Glomerular pressure increases
- Accelerates glomerular cell failure & glomerulosclerosis

Pathophysiology of DN

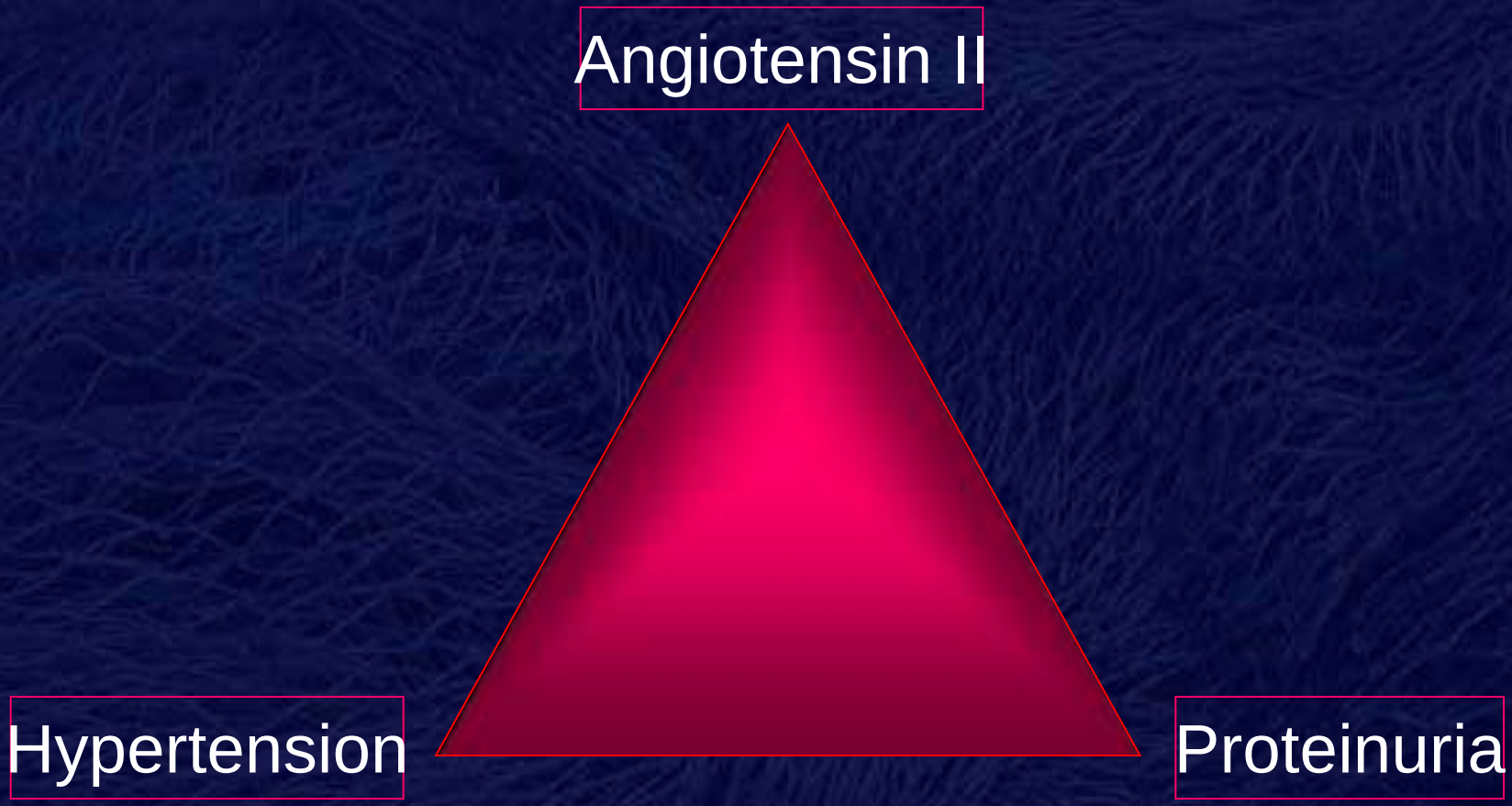
- **Sorbitol**
  - **Osmotic damage to cells**
  - **Inhibition of NO production**
  - **Increased production of free radicals**
- ***Advanced Glycation Endproducts* (AGEs)**
  - **Crosslinking reduces the flexibility, elasticity and functionality of the proteins**
  - **Initiate harmful inflammatory and autoimmune responses**
  - **Glycation has been found in connective tissue collagen, arterial collagen, kidney glomerular basement membrane**

Possible molecular mechanisms of diabetes-related complications

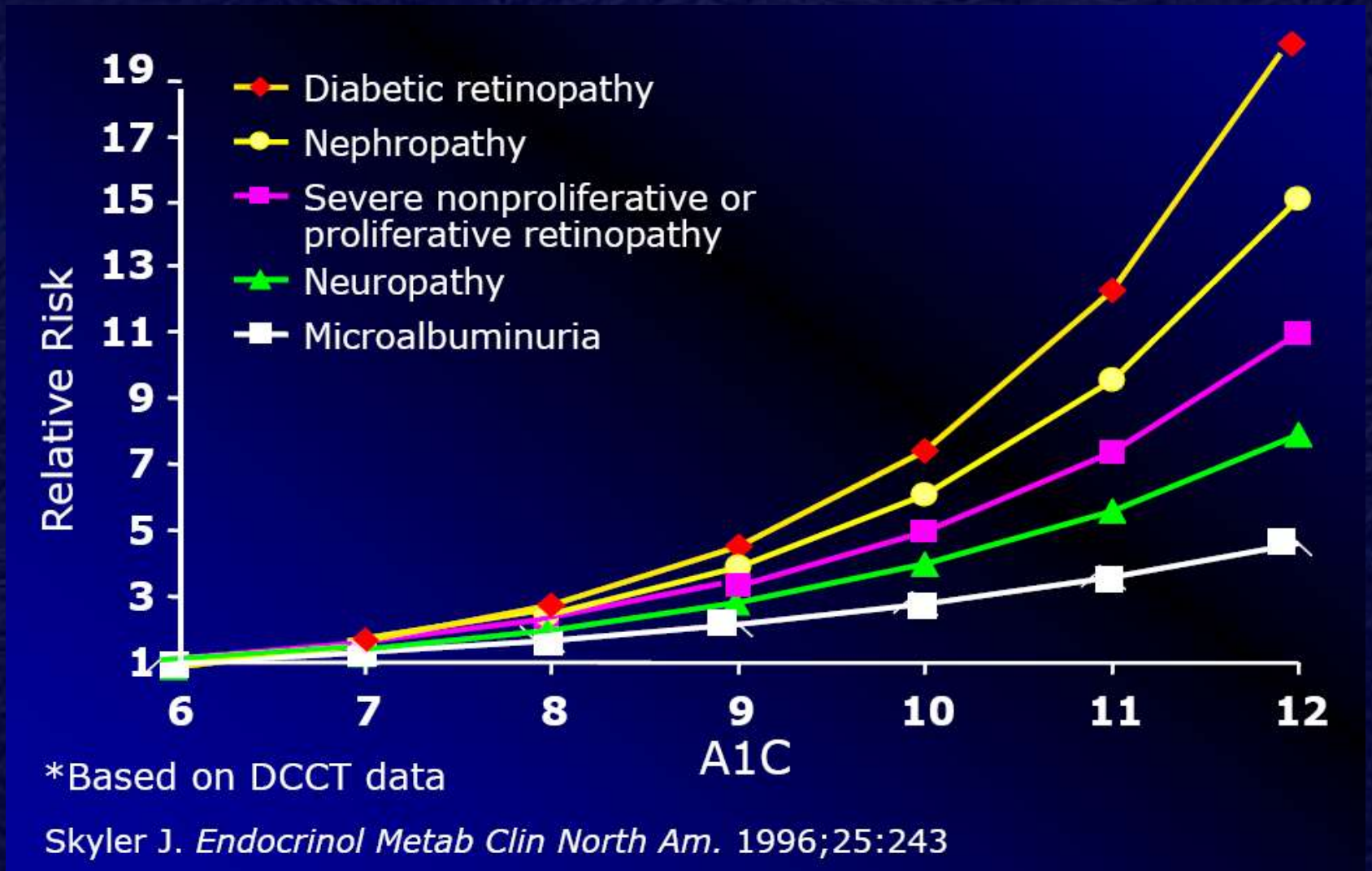


Harrison's Principles of Internal Medicine, 16th Edn

The Renal Injury Triad



Relative Risk of Progression of Diabetic Complications



Skyler J. *Endocrinol Metab Clin North Am.* 1996;25:243

Summary of Metabolic Effects of Hyperglycemia

- Oxidant Stress - related to glomerular hypertrophy and abnormal metabolism
- Non-enzymatic glycosylation of macromolecules - particularly basement membrane (BM)
- Activation of glucose metabolizing enzymes
- Cytokine and other humoral imbalances

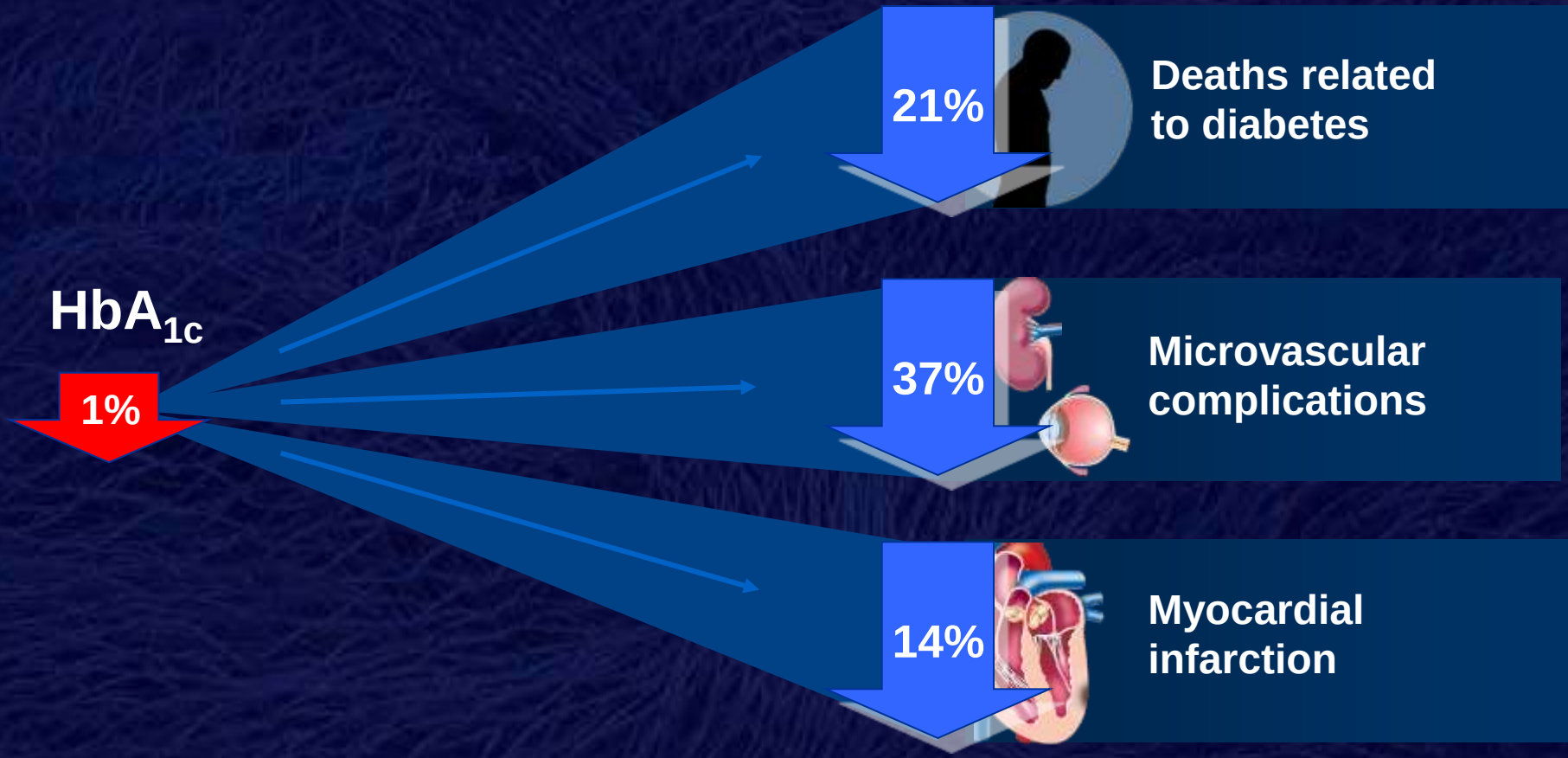
Summary of Metabolic Effects of Hyperglycemia

- ⇑ Glucagon Concentrations
- ⇑ *Transforming Growth Factor* **(TGF)-ß**
- ⇑ angiotensin II
- Abnormally regulated thromboxanes and endothelins
- Abnormal insulin like growth factor (IGF)-1
- ⇑ platelet derived growth factor (PGDF)

Effect of Glycemic Control

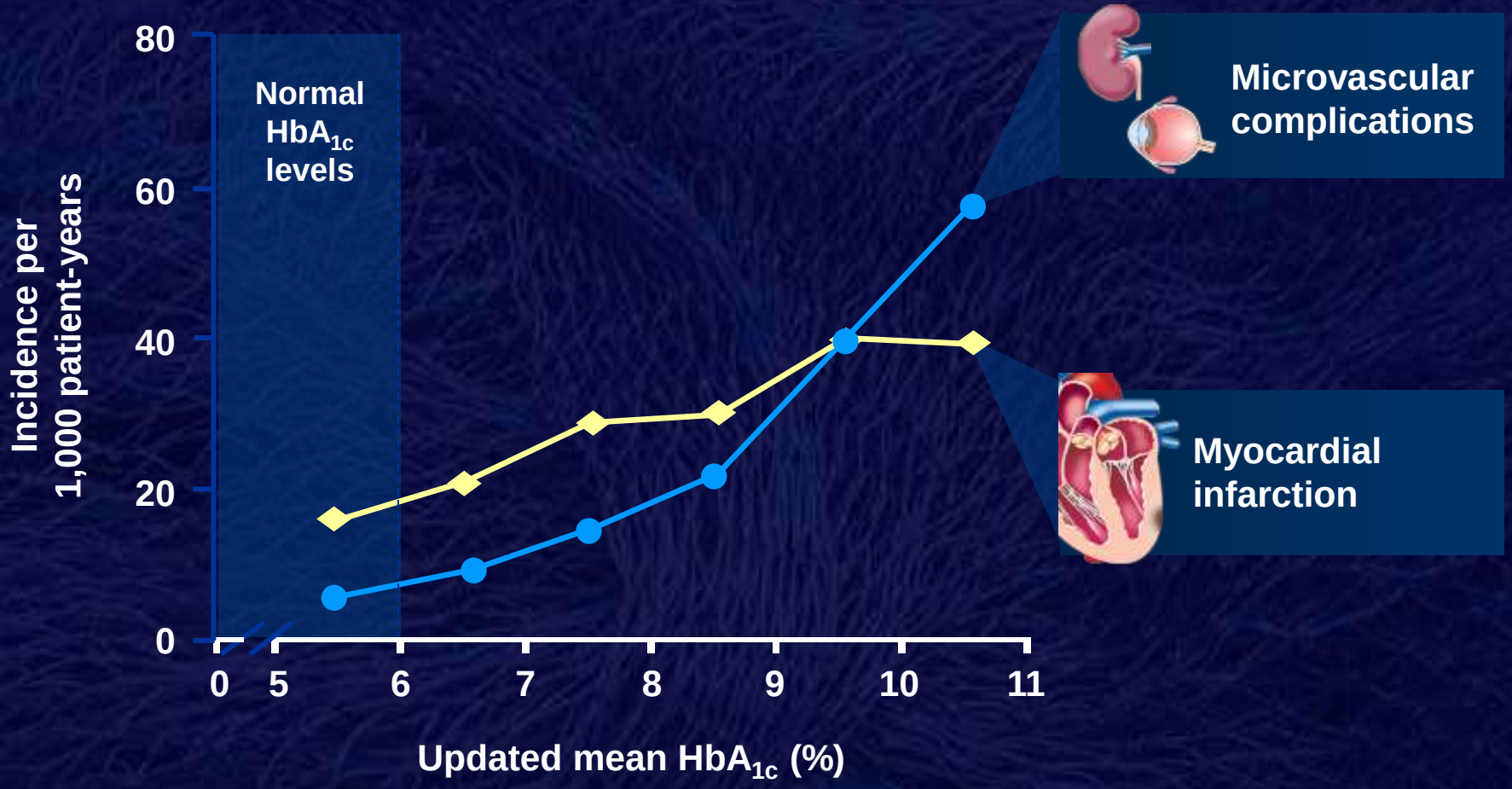
UKPDS Group: Lancet 352:837–853; 1998

Lowering HbA_{1c} reduces the risk of complications



Stratton IM, *et al*. *BMJ* 2000; 321:405–412.

Risk of complications decreases as HbA_{1c} decreases



Stratton IM, *et al*. *BMJ* 2000; 321:405–412.

DCCT: Results summary

Improved glycemic control reduced the risk of

	Relative risk reduction	
Retinopathy	**76%**	**p≤0.002**
Nephropathy	**54%**	**p<0.04**
Neuropathy	**60%**	**p≤0.002**
Cardiovascular events	**78%**	**p=0.065**

HbA1c 7% verses 9% over 9 years.
40% risk reduction of developing Microalbuminuria

Diabetes Control and Complications Trial Research Group, NEJM 329:977-986, 1993.
Diabetes Control and Complications Trial Research Group, Am J Cardiol 70:894-900, 1995.

DCCT: Microvascular Complications and Glycemic Control

TABLE 2

Adjusted risk reduction (95% CI) with intensive versus conventional treatment in the combined primary and secondary cohorts of the DCCT; the likelihood ratio χ^2 test statistic values, P values, and R^2 values for the group effect; and the percentage of the group χ^2 value explained by the log of the current mean A1C

	Risk reduction (%) (95% CI)	χ^2 test	P	R^2	% Explained by A1C
Retinopathy*					
Single three-step progression	57 (48–65)	78.3	<0.0001	5.3	95.8
Sustained three-step progression	73 (65–80)	96.7	<0.0001	6.6	96.2
SNPDR	64 (42–77)	21.0	<0.0001	1.4	99.9
Any laser	61 (34–77)	13.6	0.0003	0.9	99.5
CSME	29 (−5 to 52)	3.0	0.084	0.2	99.9
Nephropathy†					
Microalbuminuria‡	40 (23–53)	16.2	<0.0001	1.1	99.2
Albuminuria	59 (28–77)	10.0	0.0016	0.7	96.7
Neuropathy at 5 years§	68 (50–80)	27.8	<0.0001	3.9	91.8

Lachin J. Diabetes 57:995, 2008

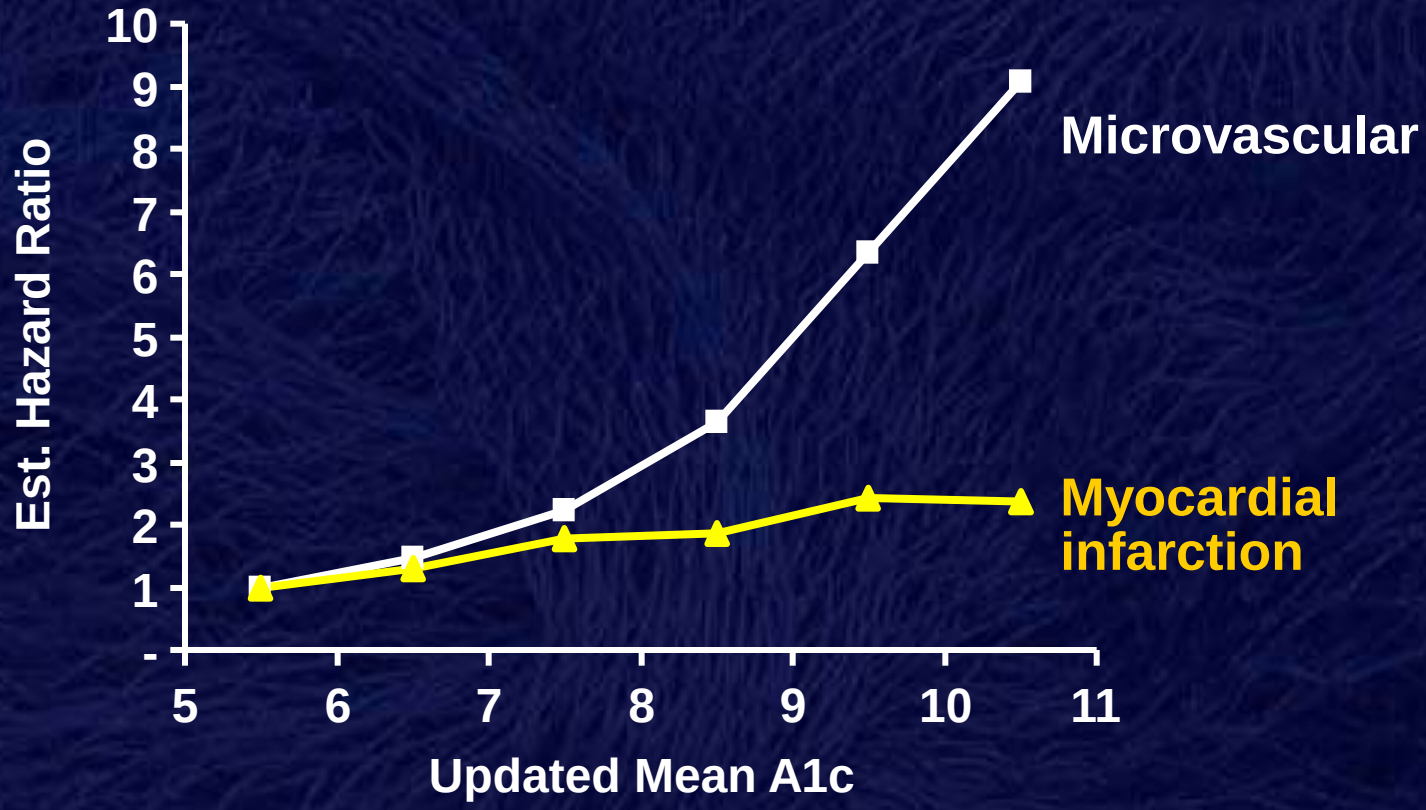
Effect of Glycemic Control in the UKPDS

Endpoints	Intensive (rate/1000 pt yrs	Conventional (rate/1000 pt yrs)	% Decrease	p value
Any diabetes related *	40.9	46	11	0.029
Microvascular	8.6	11.4	26	0.0099
Myocardial Infarction	14.7	17.4	16	0.052
Stroke	5.6	5.0	-	0.52
PVD	1.1	1.6	-	0.15

Intensive treatment with insulin and oral hypoglycaemic agents
HbA1c 7.O V 7.9 over 9 years
25-30% reduction in Microalbuminuria and 50% ↓ in the doubling of Creatinine

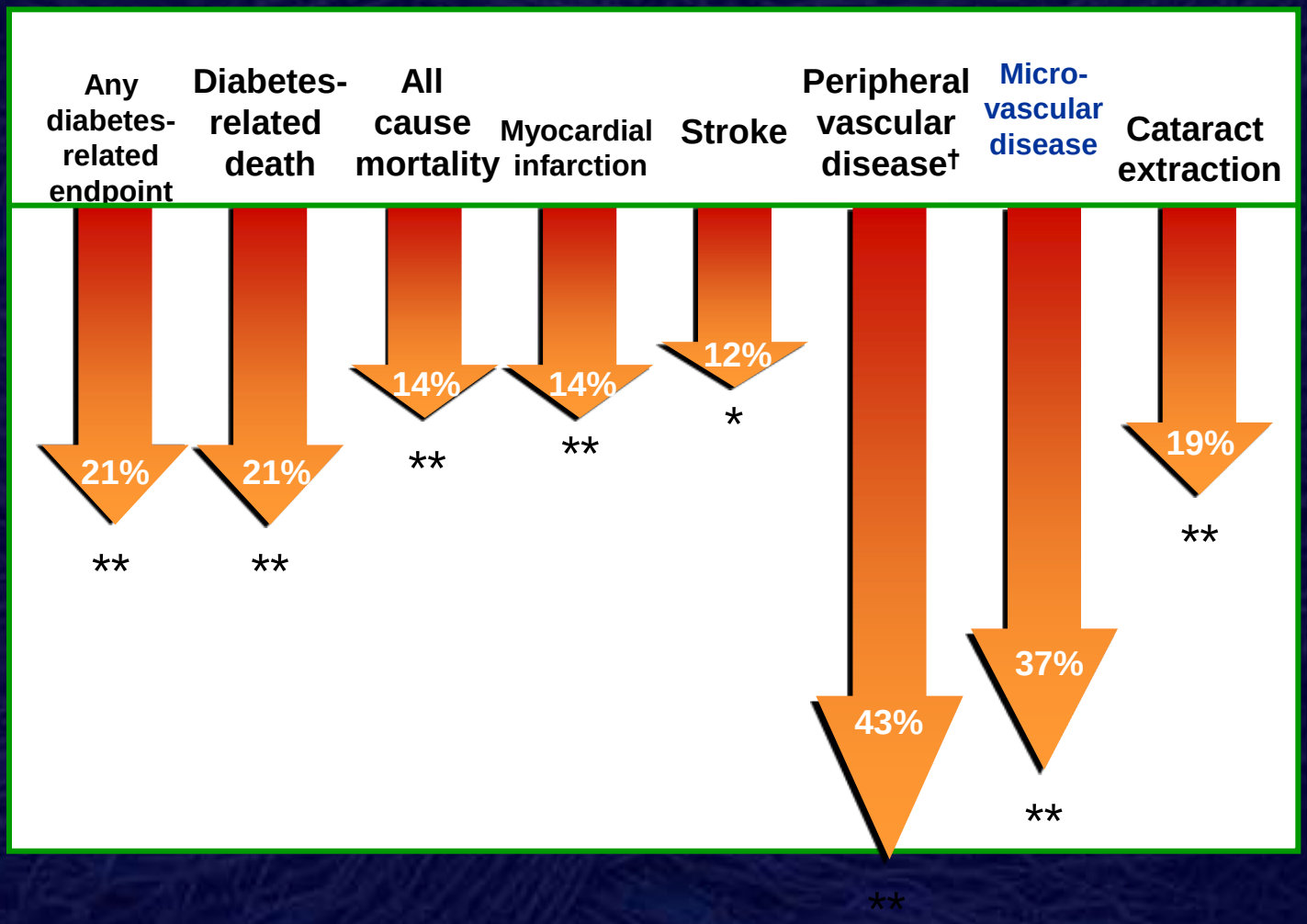
•Combined microvascular and macrovascular events
•UKPDS Group: Lancet 352:837–853; 1998

UKPDS: A1c as Predictor of Micro- and Macrovascular Disease



Stratton IM et al. *BMJ*. 2000; 321:405-412.

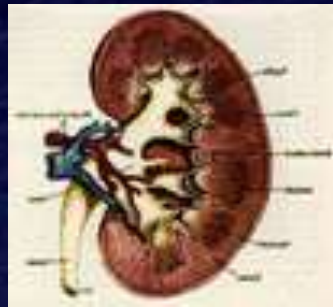
Effect of 1% Decrease in A1c on Diabetes-related Complications - UKPDS Observational Analysis



UKPDS Group - UKPDS 35: Br Med J 321:405-412; 2000

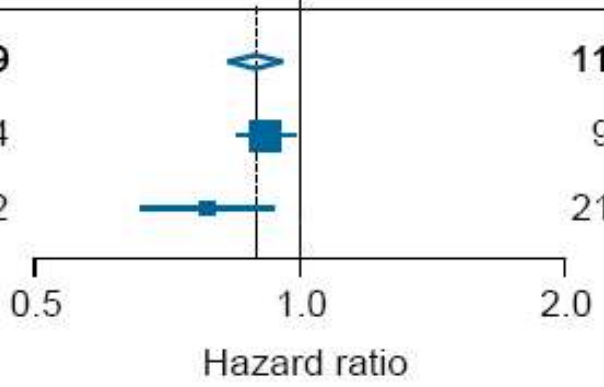
GLYCEMIC CONTROL & DN

- The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have shown definitively that intensive diabetes therapy can significantly reduce the risk of the development of microalbuminuria and overt nephropathy in people with diabetes



Renal events

	Number of patients with event: Intensive (n=5,571)	Standard (n=5,569)	Relative risk reduction (95% CI)
Total renal events	**1498**	**1669**	**11% (5 to 17)†**
New microalbuminuria	1318	1434	9% (2 to 15) ‡
New or worsening nephropathy	230	292	21% (7 to 34)***



†P<0.001

‡P=0.02

***P=0.006

Summary – effects on main efficacy outcomes

Intensive glucose control resulted in:

- 10% reduction in combined primary outcome
- 14% reduction in microvascular events
- 21% reduction in nephropathy
- No significant effects on macrovascular events
- No significant effects on all-cause or cardiovascular mortality
- Consistent treatment effects in patient subgroups

Is Insulin per se a therapeutic target?

- Slowing the progression of diabetic and non diabetic CKD with ACE-inhibitors or AT-1R antagonists is associated with an improvement of insulin sensitivity.
- But is improvement of insulin sensitivity associated with a slower progression of CKD?
  - Weight loss
  - Metformin
  - PPARγ agonists
  - Statins

Metformin in CKD

- No hypos or weight gain
- Inexpensive
- BUT:
  - Renally-excreted
  - Excess doses → anorexia, diarrhoea
  - Dose adjust to GFR: 2g to 250mg/day
  - Protocol says
    - eGFR 30 – 59 max 1gm/day
    - cease when eGFR <30 but…
  - Risk of fatal lactic acidosis if unwell

Glycemic Control

- Patients with renal impairment who are treated with an sulphonylurea should be offered education about the risk of hypoglycaemia. Clearance of both sulphonylurea and its metabolites is highly dependent on kidney function.
- Insulin doses may require reduction in association with advancing renal disease. When kidney function is impaired, the half-life of insulin is prolonged, and episodes of hypoglycaemia may occur more frequently than in patients without kidney disease

Pancreatic Transplantation

- 8 Patients with pancreas only transplants underwent serial biopsies 0,5 10 years.
- Prior to transplantation 3 normal, 3 micro 2 proteinuria
- At 10 years improved significantly the Histological changes

Evidence Based Approach
A-Level evidence

- To reduce the risk and/or slow the progression of nephropathy ,optimize glucose control .
- To reduce the risk and/or slow the progression of nephropathy ,optimize blood pressure control
- In the treatment of albuminuria/nephropathy both ACE inhibitors and ARBs can be used

Diabetic Nephropathy

Good glycemic control

Improving Outcomes
in Diabetic Nephropathy

Prevention of
Cardiovascular
Events

Prevention of
End-Stage Renal Disease

Role of Glucose Control: Summary

- Good Glycaemic control (HbA1c <7.0) only 9% of T1DM will develop ESRF after 25 years versus to controls of 40%. (Krolewski et al N Eng J Med 1995)
- DCCT: Significant reduction in progression from Normoalbuminuria to Microalbuminuria in those with tight Glycaemic control. (DCCT N Eng J Med 1993)
- UKPDS: Reducing HbA1c by 0.9% in T2DM reduces the risk of nephropathy by 33%. (UKPDS Lancet 1998)
- Euglycaemic control after Pancreas Transplantation regression of diabetic glomeruli pathology after 10 years (Fioretto et al N Eng J Med 1998)
- Overall: Intensive diabetes therapy can significantly reduce the risk of the development of microalbuminuria and overt nephropathy in Diabetics

Diabetic Nephropathy Management

Parameter	Target
Improve glycemia …….	A1c < 6.5%
Lower BP……	< 130/80 mmHg
Block RAAS……	ACEi or ARB to max tolerated
Lower LDL cholesterol……..	< 100 (70) mg/dl statin + other
Anemia management ……...	Hb 11-12 g/dl (Epo + iron)
Endothelial protection……	Aspirin daily
Smoking……	Cessation

Case #1

A 25 year old young man with a 5 year history of type 1 diabetes. His urine dipstick is negative for protein. You check a spot AM urine alb/cr ratio which is .019. His blood pressure is 112/66. His HbA1C is 6.9.

Which is (are) true?

1. The patient has early or incipient diabetic nephropathy.
2. The patient should maintain a HbA1C of less than 7 to help protect his kidneys.
3. You should start the patient on an ACE inhibitor to protect his kidneys.
4. All of the above are true.

Case #2

A 43 year old woman with a six year history of type 2 diabetes. A urine dip shows trace protein and a spot AM urine alb/cr ratio is .039. Her blood pressure is 135/80 and her HbA1C is 6.7.

Which is (are) not true?

1. You should check the patient's serum creatinine and potassium.
2. You should start the patient on an ACE inhibitor if her K+ and Cr are okay.
3. You should check a 24 hour urine for total protein and creatinine clearance.
4. The patient has overt diabetic nephropathy and should be referred to a nephrologist.

Case #3

A 60 year old with HTN, dyslipidemia and newly diagnosed type 2 diabetes. A urine dip shows 2+ protein. He has a fever and his HbA1C is 10.3. His blood pressure is 140/88. He is taking HCTZ and glipizide.

Which is (are) true?

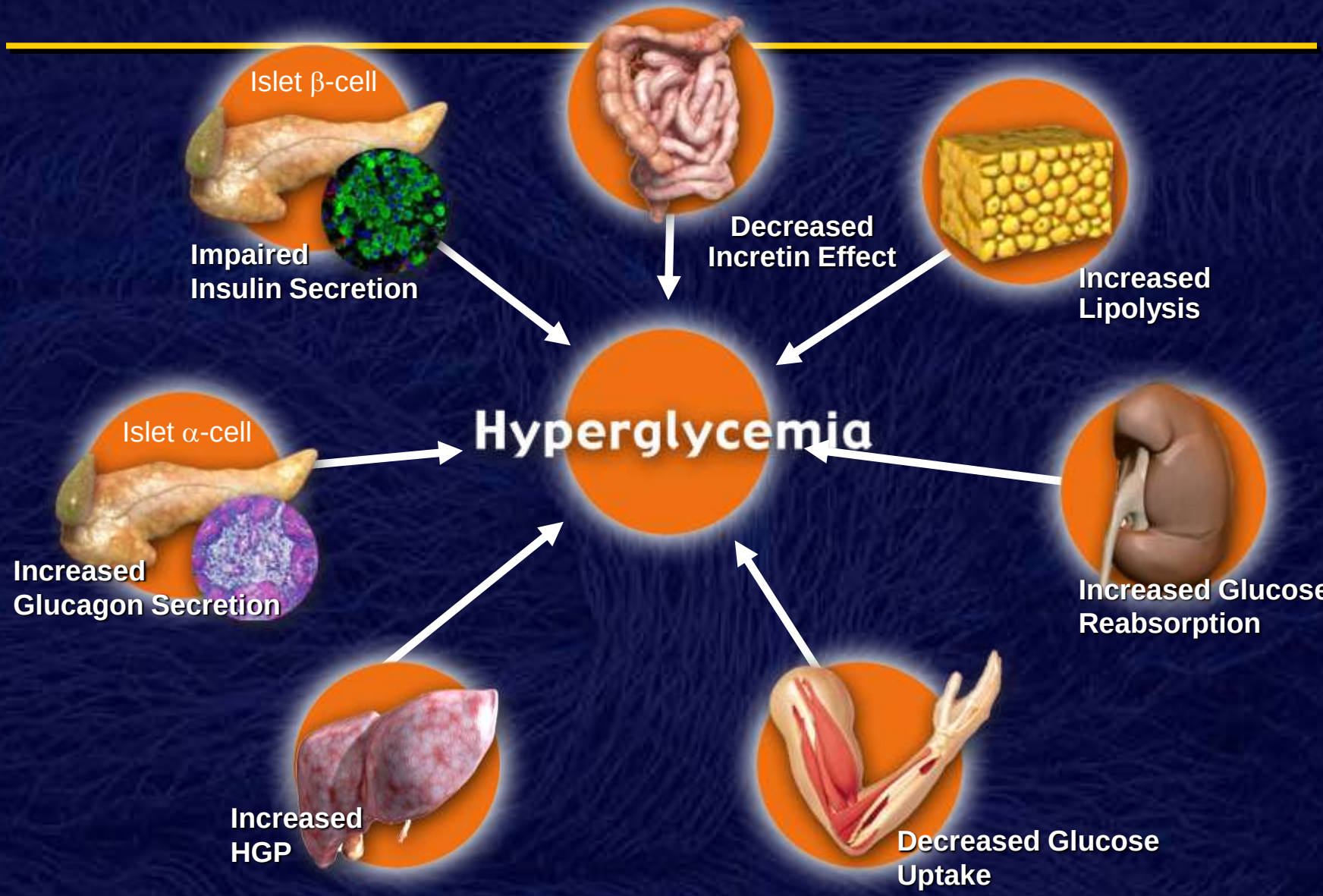
1. You should get the patient's diabetes under better control before rechecking his urine.
2. A fever will not cause proteinuria.
3. The patient's blood pressure is under good control.
4. You should check the patient's potassium and creatinine.

Case #3

Three months later with exercise, metformin and enalapril your patient's HbA1C is now 7.5 and his blood pressure is 135/85. A urine dip now shows 1+ protein.

Which is (are) true?

1. You should check a 24 hour urine for total protein and cr. cl.
2. A spot AM urine albumin/creatinine ratio correlates well with a 24 hour urine for total protein
3. The patient likely already has diabetic nephropathy and should be referred to a nephrologist.


Islet β-cell
Impaired
Insulin Secretion
Decreased
Incretin Effect
Increased
Lipolysis
Islet α-cell
Hyperglycemia
Increased
Glucagon Secretion
Increased Glucose
Reabsorption
Increased
HGP
Decreased Glucose
Uptake

Renal Glucose Reabsorption in Type 2 Diabetes

- Sodium-glucose cotransporter 2 (SGLT2) plays a role in renal glucose reabsorption in proximal tubule
- Renal glucose reabsorption is increased in type 2 diabetes
- Selective inhibition of SGLT2 increases urinary glucose excretion, reducing blood glucose
- SGLT2 Inhibition: A Novel Treatment Strategy for Type 2 Diabetes

Wright EM, et al. *J Intern Med*. 2007;261:32-43.

Diabetes and ESKD

- Reducing insulin requirements
- Difficult vascular access
- Accelerated macrovascular disease
- Advanced microvascular disease
- Frequent sepsis
- Silent ischaemia
- 2-3 x death rate vs non-DM patients

How can DM effect Dialysis?

- Autonomic neuropathy – may suffer hypotension increased by large fluid shift in HD
- Uncontrolled BSLs – may absorb some glucose in PD fluid
- Severe PVD – difficult to get vascular access for HD
- PVD may also affect peritoneum and reduce PD success
- Increased risk of infections – problem in both

Thank You